AF/1646

PATENT
Attorney Docket No. 3495.0187

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
COEN et al.	)	
	)	
Serial No. 09/501,787	)	Group Art Unit: 1646
	)	
Filed: February 11, 2000	)	Examiner: M. Brannock, Ph.D.

For: HYBRID TETANUS TOXOID PROTEINS THAT MIGRATE RETROGRADELY AND TRANSYNAPTICALLY INTO THE CNS

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir:

Enclosed is an Appeal Brief (in triplicate) in further support of the Notice of Appeal filed on December 17, 2002. The items checked below are appropriate:

1. ☒ A Petition for extension of time to extend the period for response five months to July 17, 2003, is enclosed together with a fee of $1,970.00.

2. ☒ The fee of $320.00 for filing an Appeal Brief is enclosed.

3. ☒ A check for $2,290.00 to cover the above fees is enclosed.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 16, 2003

By _____
Timothy B. Donaldson
Reg. No. 43,592

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#18 APP 3

PATENT
Customer No. 22,852
Attorney Docket No. 3495.0187

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Laurent COEN et al.	)	Group Art Unit: 1646
	)	
Application No.: 09/501,787	)	Examiner: M. Brannock
	)	
Filed: February 11, 2000	)	
	)	
For: HYBRID TETANUS TOXOID PROTEINS THAT MIGRATE RETROGRADELY AND TRANSYNAPTICALLY INTO THE CNS	)	

Mail Stop Appeal Brief--Patents
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P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Pursuant to 37 C.F.R. § 1.192, appellants submit this Appeal Brief (in triplicate) with the requisite fee under 37 C.F.R. § 1.17(c) in response to the Examiner's Final Rejection of claims 1-5, 8-11, 31, and 33-37 dated June 18, 2002. Appellants filed a Notice of Appeal on December 17, 2002. Appellants submit concurrently with this Appeal Brief, a Petition Under 37 C.F.R. § 1.136(a) and the requisite fee under 37 C.F.R. § 1.17(a)(5) to extend the time for filing this brief for five months, up to and including July 17, 2003.

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I. Real Party In Inter st

The real party in interest in the pending appeal is the assignee, Institut Pasteur, of Paris, France, by virtue of an assignment by appellants, duly recorded.

II. Related Appeals and Interferences

There are currently no other appeals and no interferences known to the appellants, the undersigned, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

III. Status Of Claims

Claims 1-5 and 8-37 are pending in this application and are set forth in Appendix I. Claims 12-30 and 32 have been withdrawn from consideration as being directed to a non-elected invention. Claims 1-5, 8-11, 31, and 33-37 stand rejected under 35 U.S.C. § 103.[1]

IV. Status Of Amendments

Appellants submitted an Amendment Under 37 C.F.R. § 1.116 on December 17, 2002. An Advisory Action was issued on February 7, 2003, indicating that the amendment after final will be entered for purposes of Appeal.

V. Summary Of Invention

The *Clostridium tetani* bacteria produces a 150 kD polypeptide known as the tetanus toxin. (Specification, p. 1.) The toxin is activated upon selective proteolytic cleavage, which generates two disulfide-linked chains: a 50 kD light chain and a 100kD heavy chain. (*Id.*) In the body, the tetanus toxin undergoes retrograde axonal transport and transynaptic transport. (*Id.* at 1-2.) Axonal retrograde transport means intraneuron

[1] The pending rejections set forth in the Advisory Action dated February 7, 2003, include claims 6 and 7. Claims 6 and 7, however, were canceled in an Amendment dated April 4, 2002. Therefore, these two claims are not addressed in this Appeal.

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transport, or transport within a neuron, such as a motoneuron. Transynaptic transport refers to interneuron transport, or transport between different neurons. (*Id.* at 12.) The protease, papain, cleaves the tetanus toxin into two fragments: the C terminal part of the heavy chain called fragment C and the complementary portion containing fragment B linked to the light chain (fragment A) via a disulfide bond. (*Id.* at 2.) Fragment C appears to retain the transport properties of tetanus toxin, while fragment A retains the toxic properties. (*Id.* at 9.)

The present invention is directed to *in vivo* methods of delivering a fusion protein into the central nervous system. (Specification, p. 4.) This is accomplished by using a fusion protein comprising a tetanus toxin fragment fused to a protein of interest, where the tetanus toxin fragment is "capable of transferring *in vivo* a protein . . . through a neuromuscular junction and at least one synapse." (*Id.*) More specifically, the claimed tetanus toxin fragment comprises fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. (Specification, p. 19.) As recited in the claims, the fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport. As set forth in claim 31, the methods of this invention can be used to treat a disease of the central nervous system by administering the fusion protein to a patient in need thereof. (*See, e.g.*, Specification, at 10-11.)

VI. Issues

(1) Whether the Examiner properly rejected claims 1-5, 8, 11, 31, 34, 36, and 37 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,780,024 in view of Fairweather et al.;

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(2) Whether the Examiner properly rejected claims 9 and 10 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,780,024 in view of Fairweather et al. and Fishman et al;

(3) Whether the Examiner properly rejected claims 1-5, 8, 11, 31, and 33-36 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,780,024 in view of Fairweather et al. and U.S. Patent No. 6,159,948;

(4) Whether the Examiner properly rejected claims 1-5, 8, 11, 31, 34, and 36 under 35 U.S.C. § 103(a) as obvious over Francis et al. in view of Fairweather et al.;

(5) Whether the Examiner properly rejected claims 9 and 10 under 35 U.S.C. § 103(a) as obvious over Francis et al. in view of Fairweather et al. and Fishman et al.;

(6) Whether the Examiner properly rejected claims 8, 11, 31, 33, 35, and 36 under 35 U.S.C. § 103(a) as obvious over Francis et al. in view of Fairweather et al. and U.S. Patent No. 6,159,948; and

(7) Whether the Examiner properly rejected claims 8, 11, 31, and 33-36 under 35 U.S.C. § 103(a) as obvious over Francis et al. in view of Fairweather et al. and Liston et al.

VII. Grouping Of Claims

Pursuant to 37 C.F.R. § 1.192(c)(7), appellants acknowledge that claims 1-5, 8, 11, 31, and 34 (Issue 1); claims 9 and 10 (Issues 2 and 5); claims 1-5, 8, 11, 31, and 33-35 (Issue 3); claims 1-5, 8, 11, 31, and 34 (Issue 4); claims 8, 11, 31, 33, and 35 (Issue 6); and claims 8, 11, 31, and 33-35 (Issue 7) stand and fall together in relation to each of the Examiner's corresponding 35 U.S.C. § 103 rejections.

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Claims 36 and 37 do not stand and fall together in relation to the Examiner's 35 U.S.C. § 103 rejections. Appellants have argued the patentability of claims 36 and 37 separately from claims 1-5, 8-11, 31, and 33-35.

VIII. Argument

A. Scope and Content of the Prior Art

The present application is a continuation application of PCT International Application No. PCT/EP98/05113 and claims priority to U.S. Provisional Application Nos. 60/055,615 and 60/065,236, filed August 14, 1997, and November 13, 1997, respectively.

The '024 patent, which the Examiner applies in the first set of 35 U.S.C. § 103 rejections, issued July 14, 1998, based on an application filed June 21, 1996. Thus, the Examiner uses the '024 patent as a 35 U.S.C. § 102(e) reference in maintaining these obviousness rejections. The '024 patent teaches a tetanus toxin C fragment recombinantly fused to a second protein (i.e., superoxide dismutase, or "SOD-1"). (*See, e.g.*, Abstract.) This hybrid protein (or fusion protein) is referred to throughout the '024 patent as the SOD-1/TTC hybrid protein. (*See, e.g.*, Col. 3, lines 66-67.) The '024 patent suggests that the SOD-1/TTC hybrid protein can be used to deliver the hybrid protein into neurons. (*See, e.g.*, Abstract.)

Francis et al., applied in the second set of 35 U.S.C. 103 rejections, was published in June 1995, and, therefore, is prior art under 35 U.S.C. § 102(b). Francis et al. teach an *in vitro* method for delivering a composition (SOD:Tet451) comprising the tetanus toxin C fragment recombinantly fused to a second protein (SOD-1)[2]. Francis et

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[2] Applicants note that the authors of Francis et al. are the same as the named inventors of the '024 patent and that the SOD:Tet451 fusion protein disclosed in Francis

al. do not disclose an *in vivo* method for delivering the fusion protein, as acknowledged by the Examiner. (Paper No. 13 at 11.)

The secondary reference, Fairweather et al., published in November 1987 and is therefore a 35 U.S.C. § 102(b) reference with respect to the pending application. Fairweather et al. describe the immunization of mice against the *Clostridium tetani* bacteria using recombinantly produced fragments of the tetanus toxin.

B. Differences Between Cited References and Claimed Invention

Independent claim 1 is directed to a method for *in vivo* delivery of a tetanus toxin fusion protein into the central nervous system ("CNS"). The other independent claim, 31, is directed to a method for treating a CNS disease using a tetanus toxin fusion protein. Claims 1 and 31 recite that the tetanus toxin portion of the fusion protein comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. Claims 1 and 31 also recite that the fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport.

The Examiner asserts that the '024 patent teaches an *in vivo* method for delivery of a composition comprising the tetanus toxin C fragment recombinantly fused to a second protein (SOD-1). (Paper No. 13 at 4.) Francis et al. disclose an *in vitro* method using what appears to be the same fusion protein. Francis et al. propose that the SOD:Tet451 fusion protein may prove useful for the targeted delivery of SOD-1 to neurons. (Francis et al., Abstract.)

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et al. appears to be the same as the SOD:Tet451 fusion protein disclosed in the '024 patent.

The Examiner acknowledges, however, that neither the '024 patent nor Francis et al. discloses a tetanus toxin fragment that includes **at least the 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C**. (Paper No. 13 at 5, 11; emphasis added). Although the '024 patent teaches that "[a]dditional amino acid residues may be present at the ends of the hybrid protein moieties without disrupting hybrid function[,]" it does not teach that such additional amino acids include at least 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C. (Col. 6, lines 38-40.) Rather, the '024 patent teaches that "[s]uch optional additional amino residues may be artifacts of the plasmid construction process, and may be left in place as a matter of convenience." (Col. 6, lines 40-42.)

The '024 patent speculates that the SOD-1/TTC fusion protein may be transported from the peripheral nervous system into the CNS "[b]y virtue of TTC-mediated uptake by neurons, retrograde axonal transport within neurons, **and** retrograde transsynaptic transfer between neurons . . . ." (Col. 4, lines 37-43; emphasis added.) But the '024 patent does not demonstrate any such transynaptic transport between neurons. Rather, appellants were the first to demonstrate *in vivo* transynaptic transport using a fusion protein containing a tetanus toxin fragment. (Examples 7 and 8 of Specification, pages 26-31.)

Fairweather et al. immunized mice with various tetanus toxin constructs, including a nonrecombinant fragment C (451 amino acids), a recombinant 441 amino acid portion of fragment C fused to part of the *E. coli* trpE protein (pTet11), and a

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recombinant fragment C plus the last 121 amino acids of fragment B (pTet18).[3] To evaluate the potential efficacy of using tetanus toxin fragments in vaccines, Fairweather et al. investigated the ability of these different tetanus toxin constructs to induce the formation of neutralizing antibodies in mice. The reference suggests nothing about using these tetanus toxin constructs to mediate *in vivo* retrograde axonal transport or transynaptic transport.

Thus, the '024 patent and Francis et al. disclose a fusion protein having the tetanus toxin C fragment recombinantly fused to a second protein. Unlike the claimed invention, however, neither the '024 patent nor Francis et al. teaches that the tetanus toxin fragment includes at least the 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C. On the other hand, Fairweather et al. disclose a tetanus toxin fragment, i.e., pTet18, comprising fragment C plus at least 11 amino acids of fragment B immediately preceding the amino terminus of fragment C. But, the pTet18 construct is not a fusion protein, as required by the claims. Moreover, unlike the claimed invention, Fairweather et al. do not teach or suggest using the pTet18 construct for *in vivo* delivery of hybrid proteins. Rather, Fairweather et al. teach using the recombinant tetanus toxin fragments for an entirely different purpose—developing vaccines.

C. Claims 1-5, 8, 11, 31, 34, 36, and 37 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,780,024 in view of Fairweather et al.

In the final Office Action dated June 18, 2002 (Paper No. 13), the Examiner rejected claims 1-5, 8, 11, 31, 34, 36, and 37 under 35 U.S.C. § 103 as allegedly

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3 The Examiner focuses on the pTet18 construct because it supplies the claimed element not disclosed in the '024 patent, i.e., a recombinant tetanus toxin fragment C **including at least 11 amino acids of fragment B**.

obvious over U.S. Patent No. 5,780,024 ("the '024 patent") in view of Fairweather et al. (Paper No. 13, pp. 4-7, ¶ 9). The Examiner maintained this rejection in an Advisory Action dated February 7, 2003 (Paper No. 16, ¶ 3.). Appellants respectfully submit that this 35 U.S.C. § 103(a) rejection is improper for the following reasons.

(1) There is no motivation to combine U.S. Patent No. 5,780,024 and Fairweather et al.

The identification in the prior art of each individual element of the claims is insufficient to establish the unpatentability of the claimed invention. Rather to establish obviousness based on a combination of elements disclosed in the prior art, the Office must demonstrate a motivation, suggestion, or teaching of the desirability of making the specific combination that the applicants made. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (reversing the Board's 35 U.S.C. § 103 rejection because there was no motivation to combine the references). The motivation to combine the references may derive from statements in the references, the knowledge of one of skill in the art, or even the nature of the problem to be solved. *Id.* at 1317. Here, no such motivation exists.

Although the Examiner acknowledges that the '024 patent does not disclose a tetanus toxin fragment that includes at least the 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C, he asserts that "it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use a Tet C fragment with at least 11 amino acids of the B fragment (as taught by Fairweather), or simply 11 additional amino acids as suggested by [the '024 patent]." (*Id.*) Thus, the Examiner asserts that the motivation to combine the '024 patent and Fairweather et al. can be found in either reference. As

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explained below, however, neither reference provides the necessary motivation to combine the reference teachings. Thus, any alleged motivation to combine these references is inappropriate hindsight reconstruction based solely on the teachings of the present specification. *See In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

(a) Fairweather et al. do not provide any motivation to combine

According to the Examiner, one of skill in the art would have motivated to modify the tetanus toxin fusion proteins of the '024 patent by adding at least 11 amino acids of the B fragment to the tetanus toxin C fragment based on Fairweather et al's disclosure of pTet18.[4] The Examiner alleges that the motivation to combine references can be found in Fairweather et al., which allegedly teach that the pTet18 tetanus toxin was easier to obtain than a protein containing only fragment C of the tetanus toxin (i.e., pTet11). (Paper No. 13 at 5). Specifically, referring to a set of experiments to determine the least amount of protein required for generating neutralizing antibodies, Fairweather et al. state that "pTet11 protein was not used in these experiments, because it was more difficult to obtain pure preparations of pTet11 than of pTet18." (Fairweather et al., p. 2543, col. 2.) From this statement, the Examiner infers that the pTet18 tetanus toxin fragment is superior to tetanus toxin containing only fragment C, such as those disclosed in the '024 patent.

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[4] As discussed above, the pTet18 construct encodes a tetanus toxin fragment comprising fragment C plus 121 amino acids of fragment B immediately preceding the amino terminus of fragment C.

There is no indication in the '024 patent, however, that the fragment-C containing fusion proteins disclosed therein were difficult to obtain. Indeed, obtaining the desired fusion protein appears straightforward. (Col. 5, lines 27-55.)

Furthermore, the pTet11 construct of Fairweather et al. is not a "protein containing only the C fragment" of the tetanus toxin, as asserted by the Examiner. The pTet11 construct is missing 10 amino acid residues of fragment C. There is no evidence that such a construct retains the properties of the full-length fragment C protein. Nor does the '024 patent describe tetanus toxin fragments having deletions of 10 amino acids of fragment C. Thus, one can not draw conclusions about the properties of pTet18 relative to the fragment C-containing hybrid proteins of the '024 patent, based on comparisons in Fairweather et al. between pTet18 and pTet11, which does not even contain a full-length fragment C.

Furthermore, Fairweather et al. actually teach away from the claimed invention. As discussed above, Fairweather et al. compared the immunological properties of pTet11 and pTet18. The pTet11 construct contained a portion of the tetanus toxin fragment C fused to the *E. coli* trpE protein. On the other hand, Fairweather et al. selected the pTet18 construct, because it "does not carry any *trpE* sequences." (Fairweather et al., p. 2542, col. 2, second full paragraph). In other words, unlike the pTet11 construct, the pTet18 construct, did not encode a fusion protein. The claimed invention, however, is directed to the administration of a fusion protein, not simply a tetanus toxin fragment. Thus, Fairweather et al., who wanted to examine the immunological properties of a recombinant tetanus toxin fragment, pTet18, which was not fused to a second protein, actually teach away from the claimed invention.

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Moreover, modifying the pTet18 construct by fusing it to a second protein, would render the pTet18 construct unsatisfactory for its intended purpose. *See* M.P.E.P. § 2143.01. If a second protein were fused to the tetanus toxin fragment of the pTet18 construct, it would defeat Fairweather et al.'s goal of measuring the antibody response to a recombinantly produced tetanus toxin fragment that was not fused to another protein. Accordingly, Fairweather et al., who investigated the immunological properties of different tetanus toxin constructs, provide no motivation to use the pTet18 tetanus construct in a method for delivering a fusion protein into the CNS, as discussed in the '024 patent.

(b) The '024 patent does not provide any motivation to combine

The Examiner further asserts that the motivation to combine the references may be found in the '024 patent based on the alleged teaching that additional amino acids may be added to fragment C as a matter of routine optimization. (Paper No. 13 at 5.) The '024 patent states that "[a]dditional amino acid residues may be present at the ends of the hybrid protein moieties without disrupting hybrid protein function. Such optional additional amino acid residues may be artifacts of the plasmid construction process, and may be left in place as a matter of convenience." (Col. 6, lines 38-42.) Thus, the '024 patent does not teach adding amino acids to fragment C as a matter of routine optimization. Rather the '024 patent indicates that additional amino acids can be present at the ends of the hybrid protein moieties, provided they do not disrupt the function of the hybrid protein. This statement in the '024 patent provides no motivation to combine the teachings of the '024 patent with Fairweather et al., particularly since Fairweather et al. is silent with respect to the function of the pTet18 construct, i.e.,

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whether the pTet18 construct "retains the neuronal binding and uptake properties of the holotoxin without the toxic domains." (Col. 1, lines 64-67.)

The Examiner also asserts that the '024 patent (Col. 5, paragraph bridging Col. 6) references the Fairweather laboratory as a source of material for practicing the invention. (Paper No. 13 at 7). Column 5 of the '024 patent cites a Fairweather et al. article that discloses the cloning and expression of the tetanus toxin fragment C. This is not the same Fairweather et al. article that the Examiner has cited in his 35 U.S.C. § 103 rejection, and therefore, does not provide the necessary motivation to combine a separate Fairweather et al. article with the '024 patent.

(2) Neither U.S. Patent No. 5,780,024 nor Fairweather et al. disclose *in vivo* transynaptic transport of a fusion protein as recited in claims 1-5, 8, 11, 31, 34, 36, and 37

Independent claims 1 and 31 recite that the fusion protein undergoes *in vivo* transynaptic transport. Neither the '024 patent nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein.

The Examiner asserts that the '024 patent demonstrates "the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to [sic, into] the CNS (e.g., from systemic administration to the brain stem, see col 1)." (Paper No. 13 at 4.) According to the Examiner, one of ordinary skill in the art would appreciate that the "in vivo retrograde transport" referred to in the '024 patent "includes both retrograde axonal transport and retrograde transsynaptic transport." (*Id.* at 6). As demonstrated in the specification, however, the art recognizes a clear distinction between *in vivo* retrograde transport and *in vivo* transynaptic transport.

> The axonal retrograde transport begins at the muscle level, where the composition of interest is taken up at the neuromuscular junction, and migrates to the neuronal body

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> of the motoneurons (which are also called the first order neurons) in the CNS or spinal cord. First order neurons mean neurons that have internalized the composition of interest, and thus in this case, correspond to motoneurons.
>
> The transynaptic retrograde transport corresponds to interneuron communications via the synapses from the motoneurons, and comprises second order neurons and higher order neurons (fourth order corresponding to neurons in the cerebral cortex).

(Specification, p. 12.)

Thus, the specification distinguishes between transport across the synapse that connects two neurons (i.e., transynaptic transport) and the uptake of compositions by a motoneuron at the neuromuscular junction followed by migration through the motoneuron (i.e., axonal retrograde transport). The '024 patent does not disclose transynaptic transport of the SOD-1/TTC fusion protein.

The '024 patent insinuates that the SOD-1/TTC fusion protein may be transported from the peripheral nervous system into the CNS "[b]y virtue of TTC-mediated uptake by neurons, retrograde axonal transport within neurons, *and* retrograde transsynaptic transfer between neurons[.]" (Col. 4, lines 37-43; emphasis added.) But the '024 patent does not demonstrate any such transynaptic transport. Column 16 of the '024 patent describes an experiment allegedly showing the uptake and retrograde axonal transport of a SOD-1/TTC fusion protein in motor neurons. Following intramuscular injection of the SOD-1/TTC fusion protein into the tongue, the fusion protein was observed in the cell bodies of the tongue motor neurons. (Col. 16, lines 14-36.) This experiment thus demonstrates uptake of the fusion protein into tongue motor neurons through the neuromuscular junction, i.e., axonal retrograde transport. But the experiment does not demonstrate transport of the fusion protein

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between two neurons. Thus, it does not show transynaptic transport of the fusion protein.

The Examiner also asserts that the *in vivo* retrograde transport of TTC was old and widely known in the art at the time the '024 patent was filed, as evidenced by Fishman et al., cited at Col. 2. line 9 of the '024 patent. (Paper No. 13 at 6.) Fishman et al. state that "[l]inkage with [tetanus toxin C fragment] also **may** enhance the stability of a chosen protein within the CNS as well as promote its spread by transsynaptic transport." (Fishman et al., p. 323; emphasis added.) This statement does not demonstrate *in vivo* transynaptic transport of a tetanus toxin fragment C fusion protein. It is mere speculation. Furthermore, as discussed in the specification, while others had shown that the tetanus toxin fragment C can undergo retrograde transport, they had not demonstrated that it can undergo *in vivo* transynaptic transport. (Specification, pp. 2-4).

Rather, appellants were the first to demonstrate *in vivo* transynaptic transport using a fusion protein containing a tetanus toxin fragment. For example, as explained in the specification, following administration of appellants' β-gal-TTC fusion protein, β-galactosidase activity was detected in the hypoglossal nucleus, i.e., the tongue motor neurons (Example 7) *and* also in connected neurons of the brainstem areas (Example 8). (Specification, pages 26-31.) Accordingly, the '024 patent does not teach or suggest transynaptic transport of the fusion protein. Fairweather et al. fail to remedy the deficiencies of the '024 patent. Thus, because the '024 patent and Fairweather et al. fail to teach every element of the claimed invention, this 35 U.S.C. § 103 rejection should be withdrawn.

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(3) Neither U.S. Patent No. 5,780,024 nor Fairweath r et al. disclose SEQ ID NO:16 as recited in claim 36

Claim 36 depends from claims 1 and 31 and recites that the fusion protein comprises an amino acid sequence comprising SEQ ID NO:16. Neither the '024 patent nor Fairweather et al. discloses an amino acid sequence comprising SEQ ID NO:16. Thus, the cited references do not teach or suggest every element of claim 36. For this additional reason, the Examiner's 35 U.S.C. § 103 rejection of claim 36 should be withdrawn.

(4) Neither U.S. Patent No. 5,780,024 nor Fairweather et al. disclose a fragment of tetanus toxin consisting of a fragment C and the 11 amino acid residues immediately preceding the amino terminus of fragment C as recited in claim 37

Claim 37 depends from claims 1 and 31 and recites that the non-toxic, proteolytic fragment of tetanus toxin consists of a fragment C and the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. Neither the '024 patent nor Fairweather et al. discloses a tetanus toxin consisting of a fragment C and the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. For this additional reason, the Examiner's 35 U.S.C. § 103 rejection of claim 37 should be withdrawn.

D. Claims 9 and 10 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,780,024 in view of Fairweather et al. and Fishman et al.

As discussed above, there is no motivation to combine the '024 patent with Fairweather et al. Similarly, Fishman et al. do not provide the necessary motivation. In addition, as discussed above, neither the '024 patent nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Fishman et al. fail to remedy the deficiencies of the '024 patent and Fairweather et al.

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Fishman et al. do not teach or suggest the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Accordingly, for this additional reason, the Examiner's 35 U.S.C. § 103 rejection of claim 37 should be withdrawn.

E. Claims 1-5, 8, 11, 31, and 33-36 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,780,024 in view of Fairweather et al. and U.S. Patent No. 6,159,948

As discussed above, there is no motivation to combine the '024 patent with Fairweather et al. Similarly, U.S. Patent No. 6,159,948 does not provide the necessary motivation. In addition, as discussed above, neither the '024 patent nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. U.S. Patent No. 6,159,948 fails to remedy the deficiencies of these references. U.S. Patent No. 6,159,948 does not teach or suggest the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Accordingly, this 35 U.S.C. § 103 rejection is improper and should be withdrawn.

F. Claims 1-5, 8, 11, 31, 34, and 36 are not obvious under 35 U.S.C. § 103(a) over Francis et al. in view of Fairweather et al.

The Examiner asserts that Francis et al. teach an *in vitro* method for delivery of a composition comprising the tetanus toxin C fragment recombinantly fused to a second protein (SOD-1)[5]. (Paper No. 13 at 10). The Examiner acknowledges that Francis et al. do not disclose an *in vivo* method for delivering the fusion protein, however, the Examiner asserts that Francis et al. propose such an *in vivo* delivery method. (*Id.* at 11). For example, the Abstract states that "SOD:Tet451 may prove to be a useful agent for the targeted delivery of SOD-1 to neurons." Therefore, the Examiner asserts that it

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[5] As noted above, the authors of Francis et al. are the same as the named inventors of the '024 patent and that the SOD:Tet451 fusion protein disclosed in Francis et al. appears to be the same as the SOD:Tet451 fusion protein disclosed in the '024 patent.

would have been obvious to one of ordinary skill in the art to use the *in vitro* method of Francis et al. in an *in vivo* method, as required by the claims, with a reasonable expectation of success. (*Id.*) Appellants submit this rejection is improper for the following reasons.

(1) Neither Francis et al. nor Fairweather et al. disclose *in vivo* transynaptic transport of a fusion protein as recited in claims 1-5, 8, 11, 31, 34, and 36

Francis et al. do not disclose *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment, as recited in the claims. The Examiner believes otherwise, relying on the following passage from Francis et al. for teaching that the SOD-1/TTC fusion protein can undergo *in vivo* transynaptic transport.

> Even with a normally functioning blood-brain barrier, the selective uptake of SOD:Tet451 by motor neurons in the spinal cord and brainstem **could be a potential route** for delivering SOD-1 to motor neurons in disorders such as ALS. Through this pathway, the hybrid protein **could** access other central nervous system neurons as well, given the ability of TTC to undergo retrograde trans-synaptic transfer.

(Francis et al., p. 15441, col. 1, first full paragraph; emphasis added.)

But the last sentence of this passage from Francis et al. refers to the ability of the tetanus toxin C fragment to undergo *in vivo* transynaptic transport, not the SOD:Tet451 fusion protein. Furthermore, as discussed in the specification, while others have shown that the tetanus toxin fragment C can undergo retrograde transport, they have not demonstrated that it can undergo *in vivo* transynaptic transport. (Specification, pp. 2-4). Rather, appellants were the first to demonstrate *in vivo* transynaptic transport using a fusion protein containing a tetanus toxin fragment. Therefore, Francis et al. do not disclose *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment, as recited in the claims. Fairweather et al. do not remedy the deficiencies of

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Francis et al. Accordingly, appellants respectfully submit that this 35 U.S.C. § 103 rejection is improper and should be withdrawn.

(2) Neither Francis et al. nor Fairweather et al. disclos SEQ ID NO:16 as recited in claim 36

Claim 36 depends from claims 1 and 31 and recites that the fusion protein comprises an amino acid sequence comprising SEQ ID NO:16. Neither Francis et al. nor Fairweather et al. discloses an amino acid sequence comprising SEQ ID NO:16. Thus, the cited references do not teach or suggest every element of claim 36. For this additional reason, the Examiner's 35 U.S.C. § 103 rejection of claim 36 should be withdrawn.

(3) There is no motivation to combine Francis et al. and Fairweather et al.

In addition, appellants respectfully assert that the Examiner has not established a *prima facie* case of obviousness because there is no motivation to combine Francis et al. with Fairweather et al. The Examiner acknowledges that Francis et al. do not teach adding at least 11 amino acids of the tetanus toxin fragment B to the tetanus toxin fragment C. (Paper No. 13 at 11.) The Examiner, however, asserts that Fairweather et al. disclose a recombinant tetanus toxin fragment C including at least 11 amino acids of fragment B (i.e., pTet18). (*Id.*) As above with the § 103 rejections based on the '024 patent and Fairweather et al., the Examiner alleges that the motivation to combine Francis et al. and Fairweather can be found in Fairweather et al., which allegedly teach that the pTet18 tetanus toxin fragment was easier to obtain than a protein allegedly containing only fragment C of the tetanus toxin (i.e., pTet11). (*Id.* at 12.)

For the reasons discussed above, establishing no motivation to combine the teachings of the '024 patent and Fairweather et al., there is similarly no motivation to

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combine the teachings of Fairweather et al. with those of Francis et al. Thus, any alleged motivation to combine these references based on the '024 patent is inappropriate hindsight reconstruction based solely on the teachings of the present specification. *See In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

G. Claims 9 and 10 are not obvious under 35 U.S.C. § 103(a) over Francis et al. in view of Fairweather et al. and Fishman et al.

As discussed above, neither Francis et al. nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Fishman et al. fail to remedy the deficiencies of these references. Fishman et al. do not teach or suggest the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Additionally, for the reasons discussed above there is no motivation to combine Francis et al. with Fairweather et al. And Fishman et al. do not provide the necessary motivation. Accordingly, this 35 U.S.C. § 103 rejection is improper and should be withdrawn.

H. Claims 8, 11, 31, 33, 35, and 36 are not obvious under 35 U.S.C. § 103(a) over Francis et al. in view of Fairweather et al. and U.S. Patent No. 6,159,948

As discussed above, neither Francis et al. nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. U.S. Patent No. 6,159,948 fails to remedy the deficiencies of these references. U.S. Patent No. 6,159,948 does not teach or suggest the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Additionally, for the reasons discussed above there is no motivation to combine Francis et al. with Fairweather et al. U.S. Patent No. 6,159,948 does not provide the necessary motivation. Accordingly, this 35 U.S.C. § 103 rejection is improper and should be withdrawn.

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I. **Claims 8, 11, 31, and 33-36 are not obvious under 35 U.S.C. § 103(a) over Francis et al. in view of Fairweather et al. and Liston et al.**

As discussed above, neither Francis et al. nor Fairweather et al. discloses *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Liston et al. fail to remedy the deficiencies of these references. Liston et al. do not teach or suggest the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Additionally, for the reasons discussed above there is no motivation to combine Francis et al. with Fairweather et al. Liston et al. do not provide the necessary motivation. Accordingly, this 35 U.S.C. § 103 rejection is improper and should be withdrawn.

To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: July 16, 2003

By: 

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Appendix I

1. A method for *in vivo* delivery of a fusion protein into the central nervous system (CNS), comprising administering to a human or an animal a fusion protein having a first protein comprising a non-toxic, proteolytic fragment of tetanus toxin (TT) recombinantly fused to a second protein, wherein the non-toxic, proteolytic fragment of tetanus toxin comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C, and wherein said fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport in the CNS of the human or animal.

2. The method according to claim 1, wherein the fusion protein is administered into a muscle.

3. The method according to claim 2, wherein the fusion protein is administered into a muscle in the vicinity of a neuromuscular junction.

4. The method according to claim 2, wherein the muscle is selected in relation with the desired area of the CNS or spinal cord.

5. The method according to claim 1, wherein the fusion protein is administered into neuronal cells.

8. The method according to claim 1, wherein the second protein is selected from the group consisting of protein SMN, BDNF (Brain-derived neurotrophic factor), NT-3 (Neurotrophin-3), NT-4/5, GDNF (Glial cell-line-derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SPI3 (Serine Protease Inhibitor protein), ICE (Interleukin-1β converting enzyme), Bcl-2, GFP (green fluorescent

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protein), an endonuclease, an antibody, or a drug specifically directed against neurodegenerative diseases.

9. The method according to claim 8, wherein the composition comprises a combination of at least two of said second proteins.

10. The method according to claim 8, wherein the second protein is located upstream from the fragment of tetanus toxin.

11. The method according to claim 8, wherein the second protein is located downstream from the fragment of tetanus toxin.

31. A method for treating a central nervous system (CNS) disease comprising:

administering to a patient in need thereof a composition comprising a fusion protein, wherein the fusion protein comprises a first protein comprising a non-toxic, proteolytic fragment of tetanus toxin (TT) recombinantly fused to a second protein, wherein the non-toxic, proteolytic fragment of tetanus toxin comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C, and wherein the fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport when administered to the patient, wherein the fusion protein effectively treats said patient.

33. The method according to claim 8, wherein the neurodegenerative disease is latero spinal amyotrophy (LSA).

34. The method according to claim 31, wherein the central nervous system disease is a neurodegenerative disease or a motoneuron disease.

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35. The method according to claim 34, wherein the neurodegenerative disease or the motoneuron disease is amyotrophy lateral sclerosis, spinal muscular atrophy, or a neurodegenerative lysosomal storage disease.

36. The method according to claim 1 or 31, wherein the fusion protein comprises an amino acid sequence comprising SEQ ID NO:16.

37. The method according to claim 1 or 31, wherein the non-toxic, proteolytic fragment of tetanus toxin consists of a fragment C and the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C.

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